REMARKS

Claims 114-168 are pending in the present application. A copy of the pending claims is attached for the Examiner's convenience. Their rejection is discussed below.

Applicants thank the Examiner and his supervisor for the interview with applicants' representatives on September 24, 2002. In the interview, applicants' remarks filed in response to the previous Office Action were discussed, and the Examiner restated his position that all of the pending claims lack enablement under 35 USC § 112, first paragraph. Applicants pointed out that a related patent has already issued with claims similar to the present claims. This supports applicants' assertion that the present application is enabling. The Examiner invited applicants to provide those remarks in written format. Such remarks are provided herein. Thus, the following remarks are in response to the Office Action, the Advisory Action and the interview.

The Invention

The present invention is drawn to methods of providing a therapeutic product to a mammal. The therapeutic product is produced by cells in which an endogenous gene encoding the protein is activated so that the protein is expressed from the genome of the cell. Activation in accordance with the invention is an *in vitro* process that involves targeted homologous recombination to place an exogenous regulatory sequence at a selected site within the genome in order to activate a selected endogenous gene. The construct used to accomplish this includes not only the exogenous regulatory sequence, but also (1) a targeting sequence, (2) an exon, (3) a splice-donor site, (4) an intron, and (5) a splice-acceptor site. The construct is introduced into a targeted cell *in vitro* by transfection (i.e., using a nonviral vector), and then homologously recombines with the cell's genome at a target site in the genome of the targeted cell. Transcription produces a transcript that contains sequence corresponding to the construct-derived exon, the construct-derived splice-donor site, the construct-derived intron, the construct-derived splice-acceptor site, and all of the exons of the endogenous gene, such that the RNA transcript encodes the therapeutic product. When this transcript undergoes splicing, the construct-derived splice-donor site interacts with the construct-derived splice-acceptor site. This results in the

splicing out of the construct-derived intron, thereby producing an mRNA that is translated into a protein. Because this entire process is carried out *in vitro*, the resulting homologously recombined cells can be cultured. Those expressing the desired level of protein can be selected, expanded, and characterized prior to implantation of the cells into the mammal. This *ex vivo* method is therefore quite different from, and eliminates many of the uncertainties of, *in vivo* gene therapy techniques.

As an initial matter, applicants point out what appears to be a source of much of the disagreement regarding enablement of the present invention: the application of the label "gene therapy" to the present methods. To that extent that it permits overgeneralization rather than careful parsing of the problems facing some forms of "gene therapy," use of this label is not helpful to the question of enablement. This is clearly illustrated by the present case. The Examiner has consistently cited various references that discuss problems (and some successes, though these the Examiner chooses to ignore) with "gene therapy" in general. When applicants have pointed out how these references do not specifically address the type of therapy to which the claims are directed, and explained why the present methods would not be expected to have the same problems as the types of therapy that <u>are</u> specifically addressed by the references, the Examiner either sidesteps applicants' explanations or addresses them without rigorous reasoning. Although applicants have supplied highly relevant evidence that the claimed methods <u>would</u> work, the Examiner appears to believe it is less persuasive than his own evidence that gene therapy in general has problems. Thus, at this point applicants urge the Examiner to rethink how the presently claimed methods fit into the broad category labeled "gene therapy," and not to generalize inappropriately.

<u>35 U.S.C. § 112, First Paragraph</u>

In the Advisory Action mailed on May 18, 2002, the Examiner maintained the rejection of claims 114-168 for alleged lack of enablement. It is applicants' understanding that the sole issue in the present case is whether methods of providing a therapeutic product to a mammal using an *in vitro* genetically engineered cell that produces the product are enabled. Applicants respectfully disagree with the Examiner's position and below provide arguments based on a related patent as well as comments on points raised in the Advisory Action.

U.S. Patent No. 5,968,502

The present application is a divisional of application serial no. 08/406,030, filed March 17, 1995 which is a continuation-in-part of U.S.S.N. 08/243,391, filed May 13, 1994 (now U.S. patent no. 5,641,670), which is a continuation-in-part of U.S.S.N. 07/985,586, filed December 3, 1992, and is also a continuation-in-part of U.S.S.N. 07/911,533, filed July 10, 1992, and is also a continuation-in-part of U.S.S.N. 07/787,840, filed November 5, 1991, and is also a continuation-in-part of U.S.S.N. 07/789,188, filed November 5, 1991. This application also claims priority and is related to PCT/US93/11704, filed December 2, 1993, and is also related to PCT/US92/09627, filed November 5, 1992. The teachings of all of these applications are incorporated by reference in their entirety into the present application (see page 1 of the present application). U.S. patent no. 5,968,502 (the '502 patent; corresponding to U.S.S.N. 08/451,894) is a divisional of U.S.S.N. 07/985,586. Thus, all of the disclosures of the '502 patent either appear in the present application or have been incorporated by reference into the present application.

Applicants point out that, like the present claims, the claims in the '502 patent are drawn to methods of providing a protein to a mammal. Specifically, the claims from the '502 patent and the present claims are similar in aspects relevant to the present enablement issue in that both the '502 patent claims and the present claims are drawn to the *in vivo* use of an *in vitro* engineered cell that produces the protein. Claim 1 of '502 is:

1. A method of providing a protein to a mammal, comprising introducing into the mammal a homologously recombinant cell which produces the protein, the homologously recombinant cell being generated by an *in vitro* process comprising:

(a) providing a cell that is autologous to the mammal, the genomic DNA of which comprises an endogenous gene;

(b) providing a DNA construct comprising:

(1) a targeting sequence homologous to a target site within or upstream of the endogenous gene,

(2) an exogenous regulatory sequence,

(3) an exon, and

(4) an unpaired splice-donor site at the 3' end of the exon,

wherein the exogenous regulatory sequence is operatively linked to the exon; and

(c) transfecting the cell that is autologous to the mammal with the DNA construct, thereby generating a homologously recombinant cell in which the splice-donor site is operatively linked to the second exon of the endogenous gene, and the exogenous regulatory sequence controls transcription of the construct-derived exon, the endogenous gene, and any sequence lying between the construct-derived exon and the endogenous gene, to produce an RNA transcript that encodes the protein, so that the homologously recombinant cell produces the protein, wherein the protein is provided to the mammal under appropriate conditions such that the protein has a desired effect.

Independent claim 42 of the '502 patent is identical to claim 1, above, except that the cell is not autologous to the mammal but is obtained from an organism other than the mammal.

The primary differences between independent claim 114 of the present application and claims 1 and 42 of the '502 patent lie in the details of the respective constructs. The construct of claim 114 comprises both a splice-donor site and a splice-acceptor site, whereas the constructs in claims 1 and 42 of '502 comprise an unpaired splice-donor site. However, the details of the construct are not at issue in this case. The sole enablement issue in the present application is related to what could be termed the "*in vivo* aspect" of the claims: providing a therapeutic product to a mammal by introducing into the mammal a cell that expresses the product of an activated endogenous gene. This aspect is common between the present case and the '502 patent. Applicants note that a U.S. patent is presumed to be valid (MPEP § 1701).

The disclosure in the present application, as filed, contains everything (and more) that was disclosed in the '502 patent. The claims of the '502 patent are presumed valid; thus, the '502 patent's disclosure is presumed to be enabling for all aspects of the methods claimed in the '502 patent, including the *in vivo* aspect. It follows that the disclosure of the present application

must be considered enabling for the *in vivo* aspect of the present claims. Withdrawal of the rejection is therefore requested.

Response to Examiner's Remarks in the Advisory Action

Applicants note that the Advisory Action failed to address all of the arguments presented in the Response mailed on April 8, 2002 (applicants' Response). The MPEP states (at § 2164.04, citing *in re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)),

> It is incumbent upon the Patent Office, whenever a rejection on this basis [lack of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

MPEP § 707.07, referring to form paragraph 7.37, notes "The examiner must address all arguments which have not already been responded to in the statement of the rejection." Applicants respectfully submit that the Examiner has not met his burden as outlined above, in that he did not provide a specific response to all arguments presented in applicants' Response. This point is elaborated below, as is applicants' belief that the Examiner continues to rely on evidence of marginal relevance in spite of applicants' submission of far more relevant evidence in support of applicants' position.

In the first paragraph of the Advisory Action, the Examiner repeated the argument that Verma et al. (at page 240, paragraph bridging the right and left columns) teaches that trial and error experimentation would be required to find an expression construct that would permit long-term expression of any particular gene. Although applicants previously pointed out that Verma et al. is referring to methods in which a viral vector was used, while applicants' method does not use a viral vector, the Examiner does not address this point at all. Furthermore, even Verma reports that viral vector infected cells continued to express Factor IX at "sustained and high levels" for more than two years after implantation in mice (page 240, col. 2). The Examiner acknowledges the Factor IX study but states

> Verma goes on to teach that finding other combinations of expression systems and genes would be 'trial and error.' This is a broadly relevant comment on the unpredictability of the art, Applicants' owm [sic] experimental results notwithstanding (Advisory Action, sixth paragraph).

Applicants are astonished at this cavalier dismissal of the relevance of applicants' own experimental results. In contrast to Verma, applicants' results were obtained using methods either within the present claims or at the very least reflecting the *in vivo* aspects at issue in the present claims. Yet the Examiner persists in dismissing applicants' evidence and even dismissing the parts of Verma that support applicants' position, and instead choosing to rely on the "trial and error" statement in Verma.

Furthermore, applicants do not understand the point that the Examiner is trying to make by referring to Verma et al. as teaching that trial and error experimentation would be required. Trial and error experimentation, even if it were necessary (and there is no indication here that it is), is not necessarily "undue." The courts have said "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Applicants have repeatedly argued that the specification provides ample guidance for one skilled in the art to practice the claimed invention. As has been explained previously, once cells have been engineered to express the desired therapeutic product using targeted homologous recombination to activate an endogenous gene, it is then merely a matter of selecting cells that express adequate levels of the therapeutic product and implanting a number of cells that produce the desired amount of therapeutic product. Applicants maintain their assertion that Verma is irrelevant to the present invention, and also that the Examiner's apparent requirements related to "trial and error experimentation" are improper.

In the Response, applicants provided the prior art example of implantation of parathyroid tissue to support their assertion that adjusting the number of implanted cells to provide the appropriate amount of a protein to an individual is not a technique new to those in the art and has been practiced successfully. The Examiner first queries whether the technique was practiced prior to the effective filing date of the present application. Applicants therefore include a copy of Senapati and Young (1990, Br. J. Surg. 77:1171-1174) (Exhibit A), which reviews the use of

the technique prior to the filing date of the application. The Examiner further questions the relevance of this evidence because "[t]he predictability and persistence of expression of the rcombinant [sic] construct is certaily [sic] at issue in the present rejection." (Advisory Action, second paragraph). This misses the point of the example. Since the Examiner had expressed the view that calculating the necessary number of cells and adjusting dosages according to the patient's response constituted undue experimentation (see Final Office Action at pages 2-3), this example was intended to demonstrate that similar methods of administering and adjusting amounts of implanted material as needed were known to those in the art.

Finally, the Examiner points out that it is merely "one procedure in one tissue type" as though that were enough to eliminate its relevance. Yet, tellingly, no evidence to support the Examiner's contrary position has been cited. The Examiner simply continues to maintain his opinion that simple arithmetic calculations and adjustments in transplant size in response to clinical results are somehow other than routine. Applicants request that the Examiner either concede the point or offer rebuttal evidence more probative than that provided by applicants.

The Examiner addresses applicants' demonstration of long-term EPO expression in mice (Example 9 of U.S.S.N. 07/787,840) by stating "these were immune-compromised animals, which do not represent a good model system for humans with normal immune systems," referring to the use of nude mice for the experiment. The text of Example 9 states

> The nude mouse provides a valuable system to study implants of genetically engineered cells for their ability to deliver therapeutically useful proteins to an animal's general circulation. The relative immune-incompetence of these animals may allow certain primary and secondary rabbit fibroblasts to survive in vivo for extended periods." (U.S.S.N. 07/787,840, page 38, lines 7-13).

Thus, the Examiner has apparently substituted his unsubstantiated opinion that nude mice are not a good model system for an explicit statement by experts that such mice do constitute a useful system for testing cells in a context similar to the present invention. Furthermore, applicants do not understand what the immune status of the test animals has to do with enablement. In order to determine whether the activated gene was expressed after the cells were transplanted, it was necessary to use a protein that wasn't naturally expressed in the test animal, e.g., a rabbit protein

expressed by gene-activated rabbit cells implanted in a mouse. To prevent the expected immunorejection of the rabbit cells, standard immunocompromised mice (nude mice) were employed. In practice, one could use syngeneic or autologous cells to avoid rejection. Alternatively, non-autologous cells could be used in situations such as vaccines where long-term expression is not needed. Regardless, dismissing as irrelevant applicants' highly relevant evidence of efficacy simply because nude mice were used seems unwarranted. It may be true that nude mice are not a relevant model system for some purposes, but the Examiner has not even come close to establishing that in the present invention. Applicants therefore question both the propriety and relevance of this aspect of the Advisory Action.

The Examiner continues to cite Orkin as teaching "that animal models were not recognized as representative model systems for humans in this art" (Advisory Action, third paragraph). Applicants have previously discussed the fact that Orkin's examples do not resemble applicant's invention (page 8 of applicants' Response) and are not relevant. These points were not addressed either in the Office Action or the Advisory Action. The Examiner instead merely states that "Orkin et al. was published well after the effective filing date of the present invention, and represents evidence as to the state of the art at the time of and even after the filing of the invention" (Advisory Action, seventh paragraph). Applicants reiterate that Orkin does not refer to the state of the art that is closest to the present invention or is even similar to the present invention. Because Orkin is not relevant, it simply doesn't matter what Orkin says about animal models, nor when Orkin was published. This was addressed in applicants' Response, where it was made clear that Orkin is discussing "direct administration" of DNA *in vivo* (see applicants' Response at page 8, first full paragraph) and the use of retroviral vectors to introduce HIV genes into "target CD4 or precursor cells." Applicants believe that the Examiner has not adequately explained why such unrelated art continues to be cited against the present invention. Furthermore, applicants' Response pointed out that none of the examples provided by the Examiner relates to *ex vivo* gene therapy. Applicants' example of prolonged expression of EPO in mice uses methods that are far more appropriate for comparison to the present methods than are the examples relied upon by the Examiner. Applicants cannot understand why the Examiner dismisses evidence that is similar to applicants' claimed method and persists in relying on evidence that is far more distantly related.

The Examiner apparently misunderstood applicants' statement in the Response that "expression in ex vivo therapies is not necessarily transient" (Advisory Action, third paragraph). Applicants were merely pointing out that even if some methods of *ex vivo* therapy that are not the same as applicants' (e.g., using viral vectors) result in only transient expression, not all methods do so. Applicants emphasize, yet again, that persistent expression is not necessarily required for their invention (e.g., applicants' Response, page 7, first paragraph) and point out, yet again, that the Examiner's focus on the issue of transient expression is inappropriate. The Examiner has not addressed this aspect of applicants' arguments, providing no response to applicants' position that even if expression is transient in some cases, it may still be useful. Few drugs, after all, provide permanent effects after a single dose. The Examiner has failed to explain why the need for repeated administrations is acceptable for, say, injected EPO, and not for the same protein delivered in accordance with the invention.

The Examiner did not find applicant's evidence of success with a Phase I clinical trial of Factor VIII expression to be supportive. The Examiner states

> [i]f trial-and-error had been employed to develop the protocol used, then whatever success the trial evinced would be considered the product of a degree of experimentation which would have been regarded as undue under 35 USC 112, first paragraph. (Advisory Action, fourth paragraph).

The reference describing this clinical trial (Roth et al., Abstract Presented at: 42nd American Society of Hematology Annual Meeting, submitted with the response as Appendix D) includes a description of the protocol. Nothing in the protocol indicates that "trial and error" were involved. Although the Examiner does not provide any definition of what exactly constitutes trial and error experimentation in his eyes, it should be evident that protocols carried out in humans cannot be performed in the cavalier way that appears to be suggested by the Examiner's invocation of "trial and error experimentation." Furthermore, applicants believe the Examiner misstates the applicable standard. As discussed above, the issue relevant to enablement is whether there was undue experimentation. There is no evidence that the clinical

trial involved undue experimentation. If the Examiner is aware of such evidence, he is asked to make it explicit. Mere speculation on the Examiner's part cannot form the basis for a rejection.

As to the Examiner's disparagement of the Roth et al. results as only a "single experiment," applicants note that as with any clinical trial, it was preceded by successful animal studies (including some reported in Roth et al.). Furthermore, it stands in stark contrast to the complete lack of any studies of comparable relevance to support the Examiner's position.

The Examiner dismisses applicants' reference to Ferber as not showing that gene therapy is routine (Advisory Action, fifth paragraph), and cites the Ferber quotation from Kay that "the persistnce[sic] issue is being solved." Applicants believe this quotation must be read in context to be understood. After stating that "[l]ong-lived gene expression has proved elusive for most nonviral vectors, in part because none of them stitch the useful gene into the genome of the host cell" (Ferber, page 1641, paragraph bridging columns 1 and 2), Ferber then proceeds to describe Kay's method which involves introducing a therapeutic gene directly into an animal. Thus, Ferber's statement the about persistence issue appears to refer to methods such as Kay's, which are not relevant to the present invention since Kay's method neither involves gene activation nor is even a method of *ex vivo* therapy. Applicants cited Ferber to provide the Examiner with an explanation for the difference between the results obtained with applicants' method and those obtained using other methods in the art.

With regard to Mountain, and as noted by the Examiner, applicants have pointed out that Mountain does not apply to *ex vivo* methods and have supported this position with carefully reasoned arguments based on the available evidence. Contrary to the Examiner's position, applicants contend that there is no reason to think that Table 4 of Mountain does comment upon *ex vivo* methods. Furthermore, the Examiner has not addressed applicants' argument that those techniques cited in Table 4 of Mountain that are typically characterized by integration into the cellular genome are not associated with "short duration" (applicants' Response, page 9). The Examiner summarily rejected these arguments by stating that Mountain "does not specify" and "there is no reason to think that Table 4 does not comment upon ex vivo methods" (Advisory Action, ninth paragraph). If this is the Examiner's position, how are applicants to reply to such references that may or may not even apply to their case? The point of such references is supposedly to provide specific support for the Examiner's position. If it is not clear what

Mountain means in Table 4, then either it is improper to cite it or further investigation should be made of the primary references used by Mountain in order to ascertain what was meant. Applicants did so and presented the results in their Response. Based upon their investigation, it is apparent to applicants that Mountain was not addressing *ex vivo* methods. Yet the best rebuttal the Examiner can muster to applicants' detailed explanation of this point is that Mountain "does not specify." If that is what the Examiner truly believes, then the rejection is faulty and should be withdrawn.

The Examiner's further point about the two post-filing date references (Miyoshi et al. and Nishi et al.) noted by Mountain is not understood. Applicants were not suggesting that those references disclose methods that are within the present claims. Rather, applicants cited them as evidence that Mountain did not believe all techniques produced only short duration of expression. As pointed out in the Response, the entries in Mountain's Table 4 that cite "short duration" as a problem were not techniques typically characterized by integration into the cellular genome. In contrast, the present invention necessarily involves chromosomal integration. It is thus more like the two "long duration" experiments disclosed in Miyoshi et al. and Nishi et al. than the experiments cited in Mountain's Table 4 as being "short duration."

Applicants previously stated that they did not see anything in Anderson suggesting that it was meant to apply to *ex vivo* methods. The Examiner apparently believes he has rebutted this by stating "Anderson is drawn to both in and ex vivo gene therapy, as is clear from the teachings of the paper in general" (Advisory Action, eighth paragraph). Applicant's statement was an invitation to the Examiner to clarify his reasons for citing Anderson, since these reasons have been unclear from the first Office Action citing Anderson. Unfortunately, merely stating "as is clear from the teachings of the paper in general" does nothing to clarify this issue. Applicants do not see how they are to respond to such a generalized remark. Once again, the Examiner is asked to provide particulars so that applicants can respond.

With respect to Anderson's reference to children effectively treated for adenosine deaminase deficiency using a gene therapy method, the Advisory Action states "Anderson found tha [sic] 'no definitive conclusion' could be drawn about the effectiveness of gene therapy, because of the other therapy being continuously applied" (Advisory Action, paragraph 8). Applicants' Response discussed this case, noting that the children received multiple types of

therapy and pointing out that "the consensus is that the engineered cells are playing some role in their improved health" (applicants' Response at page 9). In other words, gene therapy has played a role in the improved health of these children. Anderson reports that the children had circulating engineered cells at least seven years after implantation (Anderson at page 29, first column, fifth full paragraph). To the extent that these ADA cases are relevant to enablement of the present invention, it is in support of the idea that engineered autologous cells can persist long term after reimplantation, and apparently continue to produce the recombinant protein *in vivo*. The Examiner has based his rejection of the present application largely on his contention that prolonged expression would be required to practice the present invention. He also contends that transient expression is a problem with gene therapy methods in general, and so by extrapolation it would be a problem for the present invention. Applicants believe that a careful examination of the ADA data by the Examiner would further support applicants' position that the claims are enabled.

The Examiner states "the inability to provide consistant [sic], predictable, long term expression precludes the practice the invention [sic] for the types of conditions generally contemplated in the specification." (Advisory Action, final paragraph). Applicants do not understand how they can be expected to provide an appropriate response to this aspect of the rejection since the Examiner has not provided examples of which conditions he believes would not be effectively treated. In addition, applicants' question the Examiner's expertise in judging the usefulness of therapies of varying durations. Why should the necessity for occasional readministration of the cells of the invention "preclude the practice [of] the invention," when conventional drugs (including polypeptides such as erythropoietin and insulin) nearly always require frequent readministration? This point was previously raised by applicants, yet remains unaddressed by the Examiner.

In response to applicants' argument that because the method of the invention could be effectively utilized even if the implanted cells do not express the gene-activated protein for more than a short period, a lack of enablement rejection should not be based on the question of persistence, the Examiner states that the rejection has other bases as well (Advisory Action, final paragraph). Applicants were not saying this was the sole basis, only that it is a basis that was not warranted. The rationale for this position is simple: even if the Examiner were correct in his

belief that cells made and implanted in accordance with the invention would not express the therapeutic product for a long period, that would be irrelevant to enablement because long term expression is not a prerequisite for a useful method. The Examiner is asked to acknowledge this point, or to provide clear and logically reasoned arguments as to the flaws in applicants' reasoning. Merely stating that there are other bases for the rejection does not suffice.

In summary, applicants have provided ample evidence that the presently claimed methods are enabled. For example, applicants have cited evidence demonstrating

- issued claims in a prior related case (U.S. patent no. 5,968,502) that are substantially similar to the present invention in respects relevant to the present rejection and that were found to be adequately enabled;

- long-term expression (one year) of an engineered gene that was achieved in mice using an *ex vivo* method highly similar in relevant aspects to the present invention (Example 9 of '840);

- *ex vivo* methods, again similar in relevant aspects to the present invention, that resulted in successful expression in a human clinical trial (applicants' Response, page 6; Ferber);

- long-term (DITTO) persistence (at least 10 years) of *ex vivo* engineered cells in humans (in children having adenosine deaminase deficiency) (applicants' Response, page 9); and

- long-term expression of engineered cells in an animal model (Miyoshi et al., 1991, and Nishi et al., 1997, both cited in applicants' Response).

Applicants respectfully request that, in view of the arguments presented above and in applicants' previously filed Response, the rejection under 35 U.S.C. 112, first paragraph, be withdrawn.

CONCLUSION

No amendments are proposed by this Response.

Applicants submit that all of the claims are now in condition for allowance, which action is respectfully requested. This Response accompanies a Continued Prosecution Application (CPA). Enclosed is a $1960 check for the Petition for Extension of Time fee and a second check for the $1370 CPA fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07236-013004.

Respectfully submitted,

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